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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,591	08/27/2003	Noubar B. Afeyan	COTH-P02-001	7918

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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,591	AFEYAN ET AL.	
	Examiner	Art Unit	
	Mohammad Meah	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/22/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,3-5 and 14-41* is/are pending in the application.

4a) Of the above claim(s) *3,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,4,5,14-27 and 30-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

With supplemental amendment of this application, the applicants, on May 22, 2007, . cancelled claims 6-13. Therefore claims 1, 3-5, 14-41 are present for examination. Claims 3, 28-29 remain withdrawn

Applicants arguments for withdrawal of the finality of the prior office action are found to be persuasive and therefore prior office action is considered as non-final.

Claim Rejections

35 U.S.C 112

35 USC 112 2nd paragraph

Claim 16 is remain rejected under USC 112 *2nd paragraph* requirement because the recitation of the term "potent" makes these claims confusing.

Applicants arguments at page 7 of their amendments against rejection of claim 16 under 35 U.S.C 112, 2nd paragraph requirement are acknowledged but not found persuasive as explained below: Applicant appears to argue that potency is term used in biochemistry for "enzyme activity" and applicants are allowed to be their own lexicographer. Applicant may be their own lexicographer however if they choose words different from those understood in the art the burden is on the applicants to make clear what those word mean. Since these words are not standard, the specification must make it clear what they mean. There are no such explanation correlating "potency "vs. "enzyme activity" in the specification. Applicants' arguments are not enough.

35 U.S.C 112

Enablement requirement

Claims 35-36 and 38-40 remain rejected under USC 112 1st paragraph enablement requirement.

Claims 35-36 recite an adzyme that catalyze the proteolytic cleavage of any substrate polypeptide producing any product, which inhibits the substrate or the proteolytic cleavage of adzyme. The claims broadly recite the use of **any** substrate polypeptide, which is cleaved by adzyme to produce any product that inhibits the substrate binding or adzyme cleavage. The specification fails to describe how any cleavage-product of any substrate polypeptide inhibits the substrate or the proteolytic cleavage of adzyme. The specification fails to describe in any fashion the physical and/or chemical properties of the claimed class of substrates and their by-products as discussed above. As the structure of the claimed substrates and their by-products are not defined in any way, one of ordinary skill in the art would not be able to make and use any of such substrates without undue experimentation to first find what substrate and their by-product in fact fall within the claimed class. Furthermore, the claimed class of substrates and their by-products is likely to include many compounds, which one of ordinary skill in the art would be unable to make and use without undue experimentation, even if it was known or expected that the substance be within the scope of the claims.

Claims 38-40 recite an adzyme composition formulated in any way to present autocatalytic proteolysis (38) or wherein specifically a reversible inhibitor is added (39-40). However reversible inhibitors are not likely available for many protease and other means of formulating to inhibit autocatalysis are not taught.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any substrate and their by-product. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of substances having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicants arguments, on pages 8-10 of their amendment against rejection of claims 35-36 and 38-40 under 35 U.S.C 112, first paragraph enablement requirement are acknowledged. Applicants' arguments against rejection of claims 35-36 and 38-40 is not found persuasive as explained above and because these claims are directed to an adzyme wherein **any** substrate polypeptide is cleaved by said adzyme to produce any product that inhibits the substrate binding or adzyme cleavage. Therefore, as explained in the previous office action and explained above again the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and for use the invention commensurate in scope with these claims.

Applicants argue that the claimed inventions are enabled because it is well known in the art many molecules, such as cytokine, after proteolytic cleavage, inhibit the binding of the receptor. However the recitation in the claims include broad class of molecules not only cytokines and even within cytokines this is true only for specific cleavages of specific cytokines. Not all cleavage products of all cytokines and cytokine receptors antagonize the action of the receptor. Many would simply eliminate activity (in fact most cleavage probably have these

effect) and a few would not alter activity at all. Applicant suggested said explanation to other class of signaling molecules however as different signaling molecules bind or inhibit using different structural and functional moieties than that of cytokines, same argument may/or may not applies. Applicant assert that with the knowledge of structure and function of the prior art cytokines and the knowledge of applicant adzyme which catalyses proteolytic cleavage of cytokine type of polypeptide, skilled artisan is enabled to identify **any** substrate polypeptide, which is cleaved by adzyme to produce any product that inhibits the substrate binding or adzyme cleavage. It is not found persuasive because the disclosure of one or more particular instances of a particular cleavage which produces a product which acts as an antagonist is no way provides guidance for finding suitable cleavages of all cytokines much less of any substrate polypeptide. Similarly reversible inhibitors are not likely available for many proteases and recited protease inhibitors in page 10 of applicants arguments may or may not bind reversibly with any particular protease to inhibit autocatalysis. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

CLAIM Rejection - 35 U.S.C 102

Rejections of claims 1, 4, 18-21, 30-34 and 37 as being anticipated by Holvoet et al. (JBC1991, vol.266, pp 19717-19724) is withdrawn after accepting applicants arguments. However

The 102 rejections of claims 1, 4, 14, 16-25, 30-41 under 35 U.S.C. 102 Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792), of the previous office action are still remained applicable.

Claims 1, 4, 14, 16-26, 30-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis et al. (WO 00/64485) as explained by the previous office action.

Claims 1, 4, 14, 16-25, 30-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen et al. (US 2003/0068792) as explained by the previous office action.

Applicant's argument, that Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792), does not teach fusion proteins that are resistant to autoproteolytic cleavage is not found to be persuasive because although the cited references did not mention the resistively to auto proteolysis, there is no available evidence to suggest that they are labile to autoproteolysis and furthermore as their fusion proteins are stable enough to show protease activity to cleave substrate polypeptide they must inherently be resistant to self cleavage. Applicants' argument that Chen et al do not teach a fusion protein is not found persuasive. In deed Chen et at teach a fusion protein (they called it targeted protein, a chimeric protein comprising fusion of two polypeptides) comprising a "catalytic polypeptide domain (or functional domain)" fused with targeting polypeptide (a binding domain, see paragraph, 380,

430-540) wherein two ore more polypeptides comprising catalytic domain of the enzyme cross linked through N-to C- terminus of binding domain polypeptide (targeting domain). Likewise applicants argument that Davis et al do not teach a fusion protein is not found persuasive because, like applicants (applicants claims 14-15), Davis et al. fuse a catalytic domain (like protease) to a targeting moiety via chemical cross linking agent. Moreover applicants arguments that Davis "teach away" is an argument that is not applicable to an anticipation situation (see MPEP 2131.05) :

> 2131.05 [R-5] Nonanalogous >or Disparaging Prior< Art
> "Arguments that the alleged anticipatory prior art is nonanalogous art' or teaches away from the invention' or is not recognized as solving the problem solved by the claimed invention, [are] not germane' to a rejection under section 102." Twin Disc, Inc. v. United States, 231 USPQ 417, 424 (Cl. Ct. 1986) (quoting In re Self, 671 F.2d 1344, 213 USPQ 1, 7 (CCPA 1982)). See also State Contracting & Eng ' g Corp. v. Condotte America, Inc., 346 F.3d 1057, 1068, 68 USPQ2d 1481, 1488 (Fed. Cir.
> 2003) (The question of whether a reference is analogous art is not relevant to whether that reference anticipates. A reference may be directed to an entirely different problem than the one addressed by the inventor, or may be from an entirely different field of endeavor than that of the claimed invention, yet the reference is still anticipatory if it explicitly or inherently discloses every limitation recited in the claims.). A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. The question whether a reference "teaches away" from the invention is inapplicable to an anticipation analysis. Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The prior art was held to anticipate the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). >See Upsher-Smith Labs. v. Pamlab, LLC, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005)(claimed composition that expressly excluded

an ingredient held anticipated by reference composition that optionally included that same ingredient);< see also Atlas Powder Co. v. IRECO, Inc., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999) (Claimed composition was anticipated by prior art reference that inherently met claim limitation of "sufficient aeration" even though reference taught away from air entrapment or purposeful aeration.)

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4 14-17, 18 19-21, 22-27, 30 -38, 41 are rejected under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792), Guo et al. (Biotec and Biong 2000, 70, 456-463) in view of Sallberg et al. (US 6960569) or whitcomb et al. (US PAT 6406846).

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, etc) which catalyse degradation of a specific target are conjugated to binding partners wherein the binding partner is an antibody (immunoglobulin) **to the target with or without a linker and resulting fusion protein** has greater (catalytic or more than one) activity than the unconjugated molecule. The chimeric protein of Davis et al. bind to the target and the antagonize/inhibit/degrade a wide variety of receptors and/or intermediary signaling molecules

such as cytokines, EGF-like factors, etc. Davis et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectous diseases , cancer, etc.

Chen et al. teach fusion proteins wherein enzyme (beta lactamase, serine protease, protease that resistant to protease inhibitors and etc) conjugated with or without a linker to immunoglobulin or fragment or antibody to the target proteins such as kinases, lipases , and tumor or cancerous cells via with or without a linker and the resulting fusion protein bind to the target better than unconjugated enzyme. The fusion protein of Chen et al. bind to the **target and then inhibit/degrade a wide variety of targets associate with variety of hormones, receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc**. Chen et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectious diseases, cancer, etc. Although Chen et al. does not disclose the specific kinetic properties, they teach fusion protein which bind to the target 10-10000 better than unconjugated enzyme without substantially losing the enzymatic activity of the unconjugated enzyme

Guo et al. teach fusion proteins wherein enzyme (ASNase) conjugated to immunoglobulin or fragment or antibody (scFV) by a linker polypeptide $(Gly_4Ser)_3$.

Whitcomb et al. (US PAT4510251) teach mesotrypsin – a trypsin-like protease (page 10 1st paragraph) that is resistant to trypsin inhibitor and also teach that mesotrypsin rapidly degrades and inactivate zymogens and other polypeptides. Most trypsin type protease is

inhibited by PSTI whereas mesotrypsin is resistant to PSTI inhibitor). Therefore there is a **motivation** to make a fusion protein wherein the protease domain is mesotrypsin.

Sallberg et al. (US 6960569) teach fusion protein of mutated NS3/4A protease domain of HCV conjugated to antibody or other protein wherein fusion protein is resistant to proteolytic cleavage (mutation of breaking point residues of protease causes resistance to the proteolitic cleavage)

As such it would have been obvious to one of ordinary skill in the art to use mesotrypsin – a trypsin-like protease that is resistant to trypsin inhibitor as taught by Whitcomb et al. or mutation of protease as taught by Sallberg and conjugate said proteases by a linker as taught by Guo et al. to targeting domain as thought by Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792) and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide.

Applicants argument against Whitcomb et al. for not teaching stability of mesotrypsin towards proteolytic cleavage is persuasive however Whitcomb et al teach a mesotrypsin system wherein mesotrypsin is resistant to pancreatic secretory trypsin inhibitor (PSTI). PSTI inactivate protease. Therefore one knowledgeable in prior art is **motivated** to use mesotrypsin in stead of other type of protease (such as serine protease) as a catalytic domain since in in-vivo application, as taught by Davis and Chen ,compared to other proteases (as PSTI will inactivate them), mesotrypsin will remain active.

Applicants argument against combining Holvoet et al., is found persuasive and Holvoet et al., is withdrawn.

However Chen et al and Davis et al with Whitcomb et al. (US PAT4510251) is not found persuasive because as explained above Chen et al and Davis et al teach fusion protein wherein a protease domain is fused with a variety of targeting domain comprising antibody, polypeptide, etc so that the fusion protein bind to the substrate and the antagonize/inhibit/ degrade a wide variety of substrate and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Applicants argument that Chen et al do not teach a fusion protein is not found persuasive. In deed Chen et at teach a fusion protein (they called it targeted protein) comprising a "catalytic polypeptide domain (or functional domain)" fused with targeting polypeptide (a binding domain). Likewise applicants argument that Davis et al do not teach a fusion protein is not found persuasive because, like applicants (applicants claim 14-15), Davis et al. fuse a catalytic domain (like protease) to a targeting moiety via chemical cross linking agent.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-25, 30-41 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-25, 30-41 of copending Application No.10792498. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1 of instant application comprises an adzyme comprising protease as catalytic domain and claim 1 of copending application 10792498 comprises an adzyme comprising mesotrypsin a protease as catalytic domain. The remainder of these two claims is identical as are the dependent claims thereof. As such the claims of the instant application and those of the copending application differ only in the scope of protease within the claimed adzymes. Serine protease is sub species of protease. Therefore, claims 1-2, 4-25, 28, 30-41 herein are anticipated by claims 1-2, 4-25, 28, 30-41 of copending 10792498.

Claims 1, 4-25, 28-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-38, 40-46, 52-60, 66-104, 107-134 of copending Application No.10,650592. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1 of instant application comprises an adzyme comprising protease as catalytic domain fused with a targeting domain, acts on a extra cellular substrate polypeptide resulting the inhibition of receptor-mediated signaling activity of the substrate and claims 1, 4-6 of copending application 10,650592 comprises an adzyme comprising any enzyme as catalytic domain, fused with a targeting moiety, acts on any substrate (claims 1, 4), any polypeptide or extra cellular substrate polypeptide (5-6) and inhibit the substrate activity. Claim 1, 4-6 of the copending application further differ in scope from the instant claims in that claim 1 of the copending application recites specific kinetic parameters of the adzyme, claim 4 of the copending application recites that the product produced by the action of the enzyme on the substrate is an antagonist of the substrate and claim 5 of the copending application recites that adzyme is resistant to cleavage by the catalytic domain. These additional limitations are recited in the instant application only in dependent claims. However, the specification of copending application 10/650592 discloses the following specific embodiments of adzymes within the scope of claims 1. 4-6, 7-38, 40-46, 52-60, 66-104 and 107-134 therein which support the genera of adzymes recited in the claim of the copending application: prothombin/scFv αHa, trypsin/sp55. It would have been obvious to one of ordinary skill in the art to select these specific embodiments of genera of the copending application to practice the invention thereof. These adzymes anticipate the instant claims herein.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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